HOW DOES ORAL SYSTEMIC FLEA CONTROL WORK?

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Fleas are an extremely important blood sucking parasite that infest dogs and cats worldwide. Flea infestations are medically and economically important because fleas are not just irritating to dogs and cats, they can produce anemia, allergic dermatitis, carry several bacterial pathogens, and serve as the intermediate host for cestode and filarid parasites [1].

A number of field studies conducted in Australia, Europe and the United States have documented that a variety of modern topical and oral flea products can effectively eliminate flea infestations [2-14]. Compounds such as afoxolaner, dinotefuran-pyriproxyfen, fipronil (+, (s)-methoprene) imidacloprid, indoxacarb, fluralaner, lufenuron (+pyrethrin spray or +nitenpyram tablets), selamectin, and spinosad have been found in these various studies to be effective in reducing or eliminating flea infestations on naturally infested dogs and cats without the need for premises treatments [2-14].

Fluralaner, afoxolaner and sarolaner are recently introduced oral flea and tick adulticides in the isoxazoline class of drugs. These drugs work as GABA-Chloride antagonists causing over excitation of the insect and arachnid nervous system and rapid ectoparasite death [15-17]. These compounds have demonstrated rapid and persistent efficacy against fleas and multiple species of ticks].

Following the administration of a fluralaner chew, efficacy has been maintained against fleas in both field and laboratory studies for 12 weeks against fleas. A single dose of a fluralaner chew killed newly acquired female fleas rapidly enough that no eggs were laid after repeated infestations for 120 days [18]. In field studies evaluating dogs not managed with associated medications, afoxolaner and fluralaner not only managed flea infestations, but also managed clinical signs associated with FAD and pruritus [19].

Following administration of fluralaner or afoxolaner, flea populations on pets were reduced by 99.0% and 99.3%, respectively within 7 days [19]. Flea populations on the fluralaner treated dogs were 0 (100% efficacy) on days 54-60 and 82-86 after the administration of a single dose on day 0. Administration of 3 monthly doses of afoxolaner reduced flea populations by 100% on days 82-86. Flea numbers in indoor-premises were markedly reduced in both treatment groups by days 82-86, with 100% and 98.9% reductions in flea trap counts in the fluralaner and afoxolaner treatment groups, respectively. Marked improvement was observed in FAD lesion scoring, Atopic Dermatitis lesions scoring (CADESI-4) and pruritus scores with both formulations.

Spinosad first became available as an oral treatment for the control of flea infestations on dogs in late 2007. A multi-clinic, investigator-blinded study was undertaken in client-owned dogs to investigate and compare the flea control provided by 3 consecutive monthly treatments of oral spinosad (SPN) or fipronil/(s)—methoprene topical (FSM) spot-on [20]. The first household dog meeting enrollment criteria and with at least 10 fleas (whole-body flea count) served as the index dog in a household against which primary objectives were set. Stratification

was based on pruritus scores at the enrollment visit and on single or multiple pet household. Index pets were randomized to treatment with either SPN or FSM, dispensed on day 0 for at-home administration by owners. All other household dogs and cats, maximum 4 pets per household, were dispensed the same treatment as the index dog (spinetoram was dispensed for cats in SPN households). Subsequent treatments were dispensed when index dogs were returned for whole-body flea counts and pruritus-scoring at visits on days 30 and 60, with final assessments on day 90 ($\pm$ 5 days on each occasion). Primary endpoints were the number of flea-free index dogs in each group one month after the final treatment, the reduction in owner-reported pruritus, and the reduction from baseline in mean flea counts. One hundred twenty-eight index dogs were enrolled (65 in the SPN arm; 63 in the FSM arm) at 10 clinics in Florida (6), North Carolina (2), Louisiana (1), and Texas (1). On day 0, geometric mean flea counts were 57.7 (range: 10-1,469) and 44.8 (10-717) for the SPN and FSM groups, respectively. On Day 90, 55 of 58 (95%) and 21 of 55 (38%) index dogs completing the study were flea-free in SPN and FSM groups, respectively; mean SPN pruritus scores declined to 0.92 (6.67 on day 0), and to 3.83 (6.33 on day 0) for FSM; geometric mean flea counts (% control) were 0.08 (99.9%) and 5.19 (88.4%), for SPN and FSM groups, respectively. Between-treatment differences were highly statistically significant [20].

Flea allergy dermatitis or flea bite hypersensitivity is the most common dermatologic disease of domestic dogs. Cats are also afflicted with FAD, which is one of the major causes of feline miliary dermatitis. Historically, it has been said that one flea is all that is necessary to maintain the clinical signs of FAD and therefore total flea eradication is necessary. Newer adulticides such as fipronil, imidacloprid, metaflumizone, nitenpyram, selamectin, and spinosad have had a positive clinical effect on dogs and cats with FAD. However, data on flea biology and the effect of these products on flea feeding bring into question the once perceived dogma of the 'one flea bite' [21]. Adult cat fleas begin feeding almost immediately once they find a host, with many fleas feeding within minutes. In one study, 25–60% of fleas were blood fed within 5 min and in another study the volume of blood consumed by fleas
was quantifiable within 5 min Feeding is so rapid that partially digested blood can be defaecated in as little as 2–6 min after fleas acquire a host. After rapid transit through the flea, the excreted blood dries within minutes into reddish black faecal pellets or long tubular coils (flea dirt). While initiation of feeding is rapid, daily blood consumption is voracious. Female cat fleas can consume up to ten times their body weight in blood the very first day. They are on the host and peak consumption occurs within a few days at 15 times their body weight (13.6 lL) daily. With such rapid and voracious blood feeding, is it reasonable to assume that residual insecticides can truly prevent flea biting and feeding?

A study was conducted at Kansas State University, Manhattan KS, USA to evaluate the residual activity of fipronil and imidacloprid on egg production and blood feeding (unpublished data). There were two objectives to these studies 1) to evaluate if these compounds will kill newly acquired fleas prior to them feeding and 2) to determine how long these compounds will prevent viable egg production after application.

In the first experiment six cats were treated with either a fipronil spray (0.29% w/w) formulation, an imidacloprid spot-on (9.1% w/w) formulation at labeled rates or were left as untreated controls. Surprisingly when 100 Ctenocephalides felis were placed on cats 6 days after treatment with imidacloprid or fipronil, the percent of fleas that fed and consumed blood was 89 and 92%, respectively. While the adulticidal efficacy of the products was 100%, neither product killed fleas before the vast majority could bite, feed and consume at least some quantity of blood.

In another study conducted in Europe it was determined that the topical application of imidacloprid or fipronil to cats did not prevent fleas from biting and feeding. Unconfined fleas placed on cats treated with imidacloprid and fipronil had reductions in the percent of fleas blood feeding of 49.6 and 39.5%, respectively, on day seven; while reductions in percent of fleas feeding on day 28 was 0 and 3.4%, respectively. While topical applications of dichlorvos/fenitrothion or permethrin did reduce the percent of fleas feeding by greater than 80%, these compounds also did not completely prevent flea bites or feeding. The data on percent of fleas feeding on imidacloprid and fipronil treated cats in the European study differ from the data in the Kansas State University Study. This likely occurred due to the known reduced susceptibility of the KSU flea strain to imidacloprid and fipronil.

Another study conducted at KSU using dogs evaluated the ability of a 65% permethrin spot-on, a 13.8% fenthion spot-on and an 8% Chlorpyriphos collar to reduce blood feeding by fleas. At two weeks post-treatment evaluation of the blood fed status of fleas revealed that an average of 66.7% of fleas from permethrin treated dogs had fed. Fleas from chlorpyrifos collared dogs and fenthion treated dogs averaged 53.0 and 37% blood fed status, respectively. In this study the percent of fleas feeding on organophosphate and pyrethroid treated dogs was considerably higher than in the study conducted in Europe. It was later determined that the flea strain used in the KSU study was tolerant/resistant to certain organophosphates and pyrethroids.

Additional research has now been conducted to quantify the amount of blood consumed by fleas on insecticide treated cats. In this study fleas were confined for 24 hours in confinement feeding chambers attached to treated cats once a week for four 4 weeks. Confinement feeding chambers were used so that fleas and their feces could be collected for quantification and analysis. Cats were treated on day 0 with fipronil, imidacloprid, selamectin at label rates or were left untreated. In addition, another group of cats was administered nitenpyram one hour prior to each weekly infestations. After each 24 hour infestation fleas and feces were removed, microcell removed and the quantity of blood consumed and excreted was determined spectrophotometrically using the Drabkin's Reagent Method.

Fleas placed on imidacloprid and fipronil-treated cats seven days post-treatment had reductions in blood consumption of 90.78 and 69.77%, respectively. Whereas, at 14 days post-treatment fleas on fipronil-treated cats had no statistically significant reduction in blood consumption as compared to fleas on untreated controls while fleas on imidacloprid-treated cats consumed 55.73% less blood as fleas on controls. Then by three weeks post-treatment fleas on imidacloprid-treated cats had no statistically significant reduction in blood consumption as compared to fleas on untreated controls. Of particular interest was that fleas placed on cats treated orally with nitenpyram never consumed more than 1.63% (98.37% reduction) as much blood as fleas placed on control cats. Topically applied, but transdermally absorbed selamectin also had a pronounced effect upon blood consumption of fleas. Even on day 28 post-treatment there was an 88.9% reduction in blood consumption as compared to fleas on untreated controls.

As stated previously compounds such as fipronil, imidacloprid, metaflumizone, and selamectin and spinosad have had a major impact on reducing the occurrence of FAD. However, the data from the qualitative and quantitative studies demonstrates that these compounds do not stop flea bites nor completely stop flea feeding. Therefore, it appears their role in managing FAD is likely related to a decrease in prolonged flea feeding and thereby the amount of salivary protein delivered to the pet and in the long term reducing flea numbers. It is this author's opinion that FAD is related to the degree of hypersensitivity of an individual animal, the numbers of fleas feeding and amount of antigen injected. This certainly brings into question the

old dogma of a single flea bite eliciting an FAD reaction, at least in the majority of clinically afflicted animals. If a single flea bite was responsible, it appears no flea product would provide much relief, at least not until the flea population was eradicated. Also of importance to note is that regardless rather as to whether an insecticide works topically or systemically may be irrelevant in the management of fleas or FAD, since in the one study the systemically active compounds had a pronounced effect on blood feeding [21].

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